REMARKS

FORMAL MATTERS:

Claims 16-18, 22-26, 40-44, 46-50 and 57-67 are pending after entry of the amendments set forth herein.

Claims 16 and 24 have been amended. Support for these amendments can be found throughout the application as originally filed and in the following exemplary locations: page 6, lines 25 – 29; and page 17, line 27 – page 18, line 2. Claims 57-67 have been added. Support for these amendment claims can be found at page 21, lines 15-19, as well as the claims as originally filed.

No new matter has been added.

REJECTIONS UNDER §102

Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Crabtree et al. WO 95/02684 (hereinafter "Crabtree"). Applicants respectfully traverse the rejection.

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987). See also, Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991).

Furthermore, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

> "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of

circumstances is not sufficient.'" In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999).

As best understood by Applicants, it is the position of the Office that Crabtree either explicitly or inherently discloses each and every element of the above claims. Specifically, the Office indicates that Crabtree teaches administering to a host animal a heterodimer ligand comprising FK506 (or an FK506 type moiety) and CsA (or a cyclosporin type moiety). According to the Office, the binding of the FK506 conjugate to its receptor FKBP12 inherently modulates the biodistribution of cyclosporine upon administration to the host.

Applicants respectfully disagree with the reasoning and conclusion of the Office. However, solely in the interest of expediting prosecution of the instant application, Applicants have amended the claims to require that the protein target to which the drug moiety binds is a ***naturally occurring*** protein target. Specifically, independent claim 16 has been amended to recite *"wherein said drug moiety binds to a* ***naturally occurring*** *protein target and said targeting moiety is a peptidyl-prolyl isomerase ligand,"* independent claim 24 has been amended to recite *"wherein said drug moiety and targeting moiety bind to* ***naturally occurring*** *intracellular proteins and said targeting moiety is a peptidyl-prolyl isomerase ligand"* and independent claim 30 has been amended to recite *"wherein said drug moiety binds to a* ***naturally occurring*** *intracellular protein and said targeting moiety is a peptidyl-prolyl isomerase ligand."* Applicants submit that Crabtree fails to teach at least these elements of independent claims 16, 24 and 30.

Crabtree specifically teaches a method in which a ligand molecule binds and oligomerizes non-naturally occurring proteins molecules. Specifically, cells are genetically engineered, to express chimeric (***i.e., non-naturally occurring***) proteins. These non-naturally occurring proteins are designed such that they are subject to oligomerization upon administration of the ligand molecule.

> The invention involves novel chimeric (or "fused") proteins, DNA constructs encoding them, and ligand molecules capable of oligomerizing the chimeric proteins. The chimeric proteins contain at least one ligand-binding (or "receptor") domain fused to an action domain capable of initiating apoptosis within a cell, as described in detail below. As will also be described, the chimeric proteins may also contain additional domains. These chimeric proteins are recombinant in the sense that the various domains are derived from different sources, and as such, are not found together in nature (i.e., are heterologous).

(Crabtree et al., page 3, lines 24-32 (emphasis added))

> This invention thus provides materials and methods for selectively ablating cells in response to the addition of an oligomerizing ligand. The method involves providing cells engineered in accordance with this invention and exposing the cells to the ligand.

(Crabtree et al., page 9, lines 34-37 (emphasis added)).

As indicated above, the chimeric proteins described in Crabtree are recombinant proteins in which the various domains are derived from different sources not found together in nature (***i.e., non-naturally occurring proteins***). During the course of the described method, a ligand is administered which is capable of oligomerizing the non-native chimeric proteins. This allows for the selective ablation of cells engineered in accordance with the invention.

As indicated by the Office, Crabtree et al. provide a specific example in which the ligand comprises FK506 or an FK506-type moiety and a CsA or a cyclosporin type moiety. Crabtree et al. indicate that "such a ligand would be useful for mediating the oligomerization of a first and second chimeric protein where the first chimeric protein contains a receptor domain such as an FKBP12 which is capable of binding to the FK506-type moiety and ***the second chimeric protein contains a receptor domain such as a cyclophilin which is capable of binding to the cyclosporin A-type moiety***." (Crabtree et al., page 34, lines 4-9 (emphasis added)). Thus, the ligand of Crabtree, which the Office characterizes as the bifunctional molecule of the presently

claimed invention, is specifically designed such that it binds to and oligomerizes two ***non-naturally occurring*** proteins. In the context of the above example, the Office characterizes the cyclosporin A- type moiety as the claimed "drug moiety," indicating that "[t]he binding of the FK506 conjugate to its receptor FKB12 inherently modulate the biodistribution of cyclosporine upon administration to the host." (Office Action, page 2). However, as indicated above, Crabtree specifically teaches that the cyclosporin A-type moiety of the ligand is designed to bind to a receptor domain found on a non-naturally occurring protein molecule. Thus, Crabtree teaches that the alleged "drug moiety" binds a ***non-naturally occurring*** protein present in the host.

The Office asserts that "[t]he referenced heterodimer ligand is administered as a pharmaceutical composition to mammal such as a human (see page 10, line 21-25, in particular)." (Office Action page 3).

Specifically, Crabtree states as follows:

> The method thus involves exposing the cells to an oligomerization ligand capable of binding to the chimeric protein in an amount effective to result in expression of the target gene. In cases in which the cells are growing in culture, exposing them to the ligand is effected by adding the ligand to the culture medium. In cases in which the cells are present within a host organism, exposing them to the ligand is effected by administering the ligand to the host organism. For instance, in cases in which the host organism is an animal, in particular, a mammal (including a human), the ligand is administered to the host animal by oral, bucal, sublingual, transdermal, subcutaneous, intramuscular, intravenous, intra-joint or inhalation administration in an appropriate vehicle therefor. To ablate the engineered cells, one adds to the culture medium or administers to the host organism, as the case may be, a second oligomerizing ligand which is capable of oligomerizing the primary chimera.

(Crabtree et al., page 10, lines 16-28 (emphasis added)).

In describing the administration of the ligand, Crabtree indicates that host organism comprises cells which in turn comprise a ***non-naturally occurring*** protein to which the ligand,

i.e., the alleged bifunctional molecule, binds. In contrast, the claims as currently amended require that the drug moiety binds a ***naturally occurring*** protein target. As such, Crabtree fails to teach the method claimed in independent claims 16, 24 and 30.

Each of the remaining rejected claims depends ultimately from one of claims 16, 24 and 30 thereby incorporating the above limitation. As such, the above arguments apply equally to the rejection of these claims.

Furthermore, while the Office alleges that administration of the ligand as described in Crabtree (i.e., administration to a host comprising a non-naturally occurring chimeric protein molecule which binds the ligand) inherently modulates the biodistribution of cyclosporin, the Office has provided no evidence or support to show that such administration necessarily results in such modulation. The Office has also failed to show that the administration described in Crabtree necessarily results in binding of the drug moiety to a ***naturally occurring*** protein target. As indicated above, Crabtree merely discloses binding of the alleged "drug moiety" to a non-naturally occurring protein molecule. Finally, the Office has failed to show that administering a ligand according to the method of Crabtree will necessarily result in the claimed bifunctional molecule exhibiting enhanced efficacy upon administration to a mammalian host as compared to a free drug control (as indicated in claim 17) or exhibiting reduced toxicity upon administration to a mammalian host as compared to a free drug control (as in claim 18). As indicated above, inherency may not be established by probabilities or possibilities. In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999).

In addition, with respect to claims 17 and 18, the Office has providing no citation or reference to any portion of the Crabtree reference which teaches that the drug moiety has enhanced efficacy or reduced toxicity as compared to a free drug control. Nor is such a disclosure inherent in Crabtree as neither the FK506 or cyclosporin moieties of the Crabtree compounds are being used as drugs.

In view of the arguments and amendments presented above, Applicants submit that Crabtree fails to anticipate claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56. Reconsideration and allowance are thus respectfully requested.

New Claims 57 to 67 are patentable for at least the reasons provided above.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-131.

Respectfully submitted,
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